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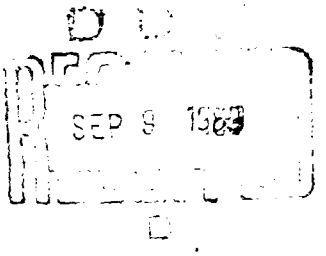

DEPARTMENT OF THE ARMY
Fort Detrick
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Translation No. T-718-1

Author: E. Strack, Der Physiologisch-Chemisch Institut der Karl-Marx Universitate (The Physiological-Chemical Institute of Karl Marx University), Leipzig.

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We have previously shown on numerous occasions that carnitine is useful as a therapeutic agent in the case of hyperthyroidism. Medically, however, it has hardly ever been used outside the local area. Additional useful data from chemical and experimental studies during the past five years have encouraged us to again discuss the problem of hyperthyroidism and carnitine. Of the many interesting observations that have been made, in this paper we will discuss only a few of the basic ones in order to familarize physicians with the problem and to interest them in the prevalent medical disorder.

The study of the localized functions of carnitine in the cells and tissues in the last few years has been pursued extensively on an international and ever-increasing scale. The new knowledge obtained from such studies even more strongly than before supports the notion that the carnitine level is capable of influencing specific processes in metabolism. From the clinical viewpoint, knowledge of the action of a substance on the organism as a whole is also of great importance. Tissue-specific substances sometimes produce surprising effects in the animal body when they are administerd in large quantities over a long period of time. Either an increasing physiological change is noticeable or regulatory as well as compensating processes are produced which have useful effects. Thus, when a substance is capable of producing numerous and graduated functional changes in the animal body, as is assumed in the case of carnitine, the quantity and kind of the level can exert a different action on the organism or a special one on a single organ. We had begun these investigations

along these lines about eleven years ago. These extensive studies were carried out in close cooperation with my pupil, Prof. Dr. W. Rotzsch.

In the earlier investigations, we had found that carnitine has an "antagonistic effect" on thyroxin. In this connection, we would like to know whether it is a question of direct or indirect influences. We have already reported on our clinical results in the case of hyperthyroidism in 1959 (1) and 1962 (2); 1 to 2 gm of carnitine administered orally over several weeks reduced a number of the symptoms associated with hyperthyroidism and noticeably improved the general state of health of the patients. Frequently, their health improved to the point where they were fully capable of working again. The small number of illnesses and the L-carnitine used by us were restricting factors. As a result, it could not always be shown that treatment with carnitine had a decisive influence on the clinical course of the disease. To be sure, DL-carnitine (1 g ≙ 0.30 MDN) is readily available and rather inexpensive. However, it is also weaker. We have not yet obtained sufficient experience with a product containing 50 % of a tissue-foreign component. In the case of one of our patients, who was treated with DL-carnitine for only a few days, the illness became considerably worsened. Previously, the symptoms had been relieved by treatment with L-carnitine. In the case of normal white rats, however, which were treated for many months with DL- or with D-carnitine, there was no visible detrimental effect on growth. Since it is the best interest of the patients and very important to us particularly to be able to elucidate the physiological modes of action of carnitine in the still unknown correlations in the organism, we could use only

the tissue-specific L-carnitine to best advantage. We produced the necessary quantities through synthesis (3) for which we would like to thank Dr. Irmgard Lorenz.

L (-) carnitine, L-4-trimethylamino-3-hydroxy-butyric acid betaine, can be obtained from natural sources or it can be synthesized. (We are grateful to VEB-Berlin-Chemie for supplying us with the starting materials for the synthesis). The price of the L-isomer would become reasonable if the demand for it in the clinics brought about its commericial production. Also, the free carnitine betaine can be easily used in injectable preparations (4). At this time as in the past, the supply of L-carnitine is still the major factor prohibiting the extensive treatment of hyperthyroidism with this compound. In order to better understand this unusual therapy with a substance which can be synthesized by the organism and which is already found in the animal's food, we should confirm the "carnitine-thyroxin" complex which we have produced experimentally. The description of the clinical observations should be withheld for another communication.

Starting in 1950, there were three groups of investigators who were studying the action of carnitine on the animal body. The American research group of Fraenkel and his co-workers suspected a vitamin activity in the meal beetle and this opened up a new direction of research concerning carnitine. The Belgian group for the most part worked with bicarnesin and DL-carnitine. Our Leipzig group carried out animal studies with the optical isomeric form of carnitine (see references 5-11).

Especially during our studies with rats, we found that dystrophic individuals reacted more clearly to large doses than did

normal animals. Similar individual reactions were seen by the Belgian investigators. Small animals were observed also which reacted to doses only slightly larger than the preceding dose which could have been found in the usual food. We suspect that either these individuals did not have a sufficient supply of carnitine or that specific influences disturbed the function of carnitine in metabolism. This carnitine supply inhibits the faulty performance.

Thus, it is clear that weight-reducing hyperthyreosis reacts to carnitine administration alone with a considerable increase in weight. A patient with hyperthyroidism, who was affected only slightly by carnitine except with regard to diminished basal metabolism and improved nervous manifestations, showed a weight increase of nearly 10 kg over a 2-month period when treated daily with 2 gm of carnitine (Medical University Clinic of Charity, Berlin, Director, Dr. F.-H. Schulz).

We proved our hypothesis concerning the contrasting influences of thyro-hormone and carnitine in vitro and in vivo. We employed both warm-blooded and cold-blooded animals in our studies. In these, a disruption of the metabolism can be easily produced by the introduction of thyroxin. This was measured using two well-known and unrelated criteria. It was shown in a series of experiments that the addition of carnitine to the environmental water of tadpoles on a regular basis compensated strongly for the reduction in growth due to thyroxin. However, the accelerated metamorphosis was not noticeably retarded. This dualistic action by carnitine may occur as a result of the unfavorable nature of the carnitine supply. Later, however, we found a similar behavior

in the case of hyperthyreoses. Those symptoms which were the result of altered metabolic processes improved while the symptoms based on the tissue matrix, such as struma and exophthalmus, were hardly affected. For that reason, we spoke confidently of the carnitine as being a "partial antagonist" of the thyroid hormone. Whether this limitation in the mode of action actually exists, larger clinical trails with longer observation periods could determine. We concluded further that weak carnitine could mutually regulate the physiological metabolism of both substances even in their functions and reduced the action of the thyroid hormone. We certainly had indications of the influence of carnitine in the observation that in a series of hyperthyreoses, the excretion of trimethylamine and trimethylamino oxide in the urine was shifted from normal (1,2) thus indicating an increased degradation of quaternary nitrogen compounds. Carnitine belongs to this group of chemical compounds. This fact served as the starting point for additional biochemical and biological studies in which we studied the behavior of both parameters, thyroxin and carnitine, together. One of these studies on the metabolism and blood as well as thyroxin will be mentioned briefly.

Our observations on animals were highly interesting since carnitine influences the metabolism of mitochondria which are the areas of oxidation where energy-producing and synthetic processes occur. It is also known that thyroxin alters these <u>in vitro.</u> Probably, a large portion of the metabolic-related characteristics observed in cases of hyperthyreoses have their origin there. Using the method of Warburg, we were able to measured increase O_2

consumption of isolated mitochondria when carnitine was added (12). This could not be confirmed, however, polargraphically using the vibrating Pt-electrode. This satisfied us when prerequisites for the measurements were worked out (13). Meantime, Bremer (14) during studies in 1962 described for mitochondria from almost all tissues increased O_2 consumption as measured by the Warburg method upon addition of carnitine or acetylcarnitine in vitro.

Although the effect can be regularly reproduced, it appears to us that it is associated with a physiological process which had not yet been uncovered. We first held this to be the case when we noted increased O_2 consumption with mitochondria from normal rats which had been injected with carnitine several hours before (12). By this time, we had confirmed the severe optical specificity for L-carnitine and its acetyl derivative which could only be employed in pure form in the in vitro studies.

Although the effect can be regularly reproduced, it appears to us that it was associated with a physiological process which had not yet been uncovered.

By 1955, Friedman and Fraenkel (15) had found an acetyl-transferring enzyme for carnitine. At the same time Fritz (16) had found that the addition of carnitine-rich muscle extracts to tissue homogenates increased fatty acid conversion. These observations represented the starting point for the reactions involving carnitine as an acyl carrier in the mitochondria which were studied by these and other authors. Carnitine can accept as esters of its hydroxyl group fatty acids from coenzyme A and then donate them again. The energy requirements for this are available and the necessary enzyme systems were isolated and characterized. The

muscles produce the principal quantity of calories in the body and consequently determine essentially the basal metabolism. The muscles also contain a great deal of carnitine. Interruption of its range of action should for that reason be easily detected here. The quantity of B-vitamins in muscles was determined for normal and thyroxin-treated animals. In the case of rats, thyroxin increased the B-content (17) while carnitine depressed it (18). Carnitine normalized again the vitamin B level which had been increased by thyroxin. Since the B vitamins are coenzymes in the energy-related processes, then the increases and decreases in thei concentrations are expressed by altered reaction rates in the muscle. The muscle from hyperthyreotic patients is likely to behave in a similar manner as suspected by the increased basal metabolism associated with cases of this disease. The decrease of the vitamin B level and the conversion by carnitine were then studied in those acyl carrier functions whereby oxidation of fatty acids occurs in the mitochondria. Under hyperthyreotic conditions, the catabolism was unbalanced but was again corrected by carnitine.

The behavior of the P/O quotients of the mitochondria points to the same conditions. Upon addition of carnitine <u>in vitro</u>, the quotient decreases as an expression of increased O_2 consumption without any appreciable change in the concomitant ATP production. In the case of throxin administration, the P/o quotient is decreased by a reduced ATP synthesis eventhough there is increased O_2 consumption. If one offers carnitine to thyroxin-intoxicated mitochondria, the O_2 consumption is not increased but the ATP synthesis is improved and consequently the P/O quotient increases (12).

effects in either normal control subjects or in cases of hyperthyreoses. Also, these are scarcely to be expected under the circumstances, as the acute toxicity of carnitine is quite low. In the case of the mouse, it amounts to 13.5 mg per gm of body weight (20), and in the case of the rat, it is even lower. Our doses for hyperthyreotic patients amounted to 1 to 3 gm of carnitine per day. In comparison to the mouse, this amount for only a fraction of a percent of the acute toxic doses. In addition, the doses were administered orally and distributed over the entire day.

We have hitherto never seen chronic derangements or secondary effects. Carnitine is only in the beginning of the treatment accumulated in small portions in the body, probably through the refilling of physiological depots. By secretion and destruction, the body can easily remove any unwanted excesses. In comparison to the presence of about 15 gms of carnitine in the human body, the 3 gm daily doses somstimes appears relatively enormous. However, the half-life of the carnitine is about 2 to 3 months. The carnitine in the body is quite stable and is altered only gradually by the introduction of carnitine. It was found that when 0.5 gm amounts of carnitine labeled with N^{15} were administered daily into a study patient, within three days, all of the N^{15} was again to be found in the patient's urine. It had passed through without mixing noticeably with the carnitine in the body. This suggests that the physiological tissue carnitine is bound in some special manner and that there may be a very characteristic mechanism of synthesis present. In the case of normal rats, a month-long

administration of daily doses of carnitine containing 3 mg of carnitine per grm of body weight caused essentially no changes. Only one of the normal animals responded with a strong increase in body weight.

Thyroxin and carnitine also have contrasting effects on protein metabolism. Thyroxin increases the N-turnover whereas carnitine decreases it.(10). This is particularly noticeable when treatment is first initiated. The protein metabolism of rats, which was increased by thyroxin, was again returned to normal by the administration of carnitine. This effect of proteins gives us some idea concerning the nature of the favorable influence of carnitine on the sensitivity of hyperthyreoses toward food proteins. Such an influence can also be used to explain the fundamental observations of Fraenkel (6) and other authors, In the case of meal beetles placed on a carnitine-free diet, it was observed that in the transition from the larval stage to the beetle stage, only a defective body could be produced and that the insect was incapable of survival. The proteins that are synthesized in the larvae in the absence of the "protective action" of carnitine appear to be unsuitable for the new life cycle stage. Since protein synthesis in this animal population is not sufficiently improved by carnitine, it is suggested that still other factors, like trace elements, are also involved.

In addition, the transaminases were also implicated with the protein metabolism. In the case of rats receiving thyroxin, they were elevated in the tissues (23) and in the blood (24). Carnitine

decreased the elevated blood levels (19). The transaminases also behave in a similar fashion in the case of hyperthyreoses. The transaminases of normal rats also respond to carnitine. The transaminase activity is altered under a variety of experimental conditions and is dependent in characteristic ways on the quantity of carnitine administered and the time of administration. (19). At certain levels of carnitine, the blood activity of the transaminases remains for the most part unaffected. Probably in this case, however, the carnitine exerts the same effective influence as the normal reaction. Increasing amounts of carnitine results in the production of a biphasic response curve. Evidently, for the complete activity of carnitine to be expressed, a relatively large dose over many days is required.

Furthermore, we found in the case of rats that carnitine influences the creatine production and the level of ATP in the skeletal muscles. Single doses increase the level of ATP and creatine phosphate (25). In the case of hyperthyreoses, carnitine administration increased the diminished productive power of muscles and lessened the tendency towards fatique. Probably, these improvements had as their basis the same metabolic effects as had been previously observed in rats. Our observations indicate in this respect that carnitine is capable of acting on metabolically-associated muscule ailments. In fact, inhibition of swallowing as a result of atrophy of the esophagus muscles in hyperthyreotic patients is quickly reduced by carnitine (Medical Clinic of Carl Marx University, Leipzig, Director: Dr. R. Emmrich).

Other metabolically dependent symptoms in hyperthyreoses were considerably and regularly improved by carnitine administration. Elevated body temperatures decreased to normal levels, and the tendency to perspire subsided. Tachycardia was reduced and a normal heart beat partially restored. Arrhythmia absoluta disappeared.

The role of cholesterol which is reduced in hyperthyreoses increases with carnitine administration. Also, this effect can be explained by the carrier function of carnitine for fatty acids. Through its derivative, acetylcarnitine, acetyl groups can be transferred which are essential for cholesterol synthesis. In a similar manner, they can also influence the hormone levels of the suprarenal capsule. This results in the favorable activity of carnitine in hyperthyreoses. The improvement by carnitine of nervous symptoms, restlessness, and overexcitability in hyperthyreoses is less openly connected to metabolism. These are easily influenced favorably at the beginning of carnitine administration. Likewise in mice treated with carnitine, we could detect a suppression of nervous reaction states (unpublished).

The total iodine level in the blood is elevated during hyperthyreoses; carnitine administration usually reduces it (1,2). We studied this effect using Iodine ^{131}.

Serum proteins *in vitro* bind carnitine strongly when it is added. The alpha- and pre-albumin fractions are involved. The L-isomer is bound slightly better than is the D-isomer (26). In the same region, thyroxin is also bound. It cannot be detected *in vitro*, however, that carnitine addition suppresses protein-bound iodine. On the other hand, if one injects Iodine ^{131} into

rats after carnitine (nistration, inorganic iodine was increased in the serum for many hours after while the organic-bound iodine was decreased (27). It was found that up to 20 hours after Iodine ^{131} administration, in the inter-alpha region of the rat serum, only slight activity could be detected when the animals were kept on carnitine treatment. In the case of rats receiving D-carnitine, the levels were the same as those in animals which had not received any carnitine (28). The shift in the iodine fraction of the serum indicates that carnitine hinders the formation of iodine-hormone in the thyroid gland. We could detect that Iodine^{131} uptake remains delayed if the rats previously received repeated doses of L-carnitine at a level of 1 mg per gm of body weight. Up to about ten hours, the activity of rats previously treated with L-carnitine was about one-third less than that of rats which did not receive carnitine. After about 40 hours, the effect of carnitine begins to decrease (27). These observations show that carnitine not only exerts an influence on the activity of thyroid hormone in the peripheral tissues, but also can be active at the center of hormone function.

DISCUSSION AND CONCLUSIONS

If one examines closely the prevailing effects of carnitine treatment in the case of hyperthyreotic illnesses and then considers the possibilities offered by treatment with carnitine or one of its derivatives, then one is completely justified in considering it to be useful and productive for this purpose. Carnitine can be taken orally with good results. The body can easily eliminate an excess of carnitine. Because of an unusually slight toxicity, heavy doses of carnitine do not pose a problem.

Moreover, it is within the power of the physician to alter the time and degree of activity. In the case of the introduction of carnitine, one avoids violent interferences in the labile functions of the diseased organism in contrast to many other means of treatment.

With reference to the derangements in metabolism brought about by the elevated release of thyroid hormone, carnitine will serve as a material with an antagonistic effect. Its physiological site of action for the most part is the mitochondria of the cells. This is also the case with the thyroid hormone. In this respect, the ideal principle of thearpy can be realized, that is, to counterbalance the malfunction by means of a physiological partner. Unequivocal statements, however, can be made only after the underlying modes of actions of both substances at the physiological site have been elucidated more clearly than is now the case. Also, in the case of carnitine, the activity is, as in the case of thyroxin, strongly dependent on the size of the dose and the duration of treatment.

The limitations encountered in applying the experimental resulted obtained from animal studies to human thyreoses are true also in the case of the transport process in blood and for the behavior of the thyroid gland during carnitine administration. For the most part, these have been studied in rats. Our studies have shown us only that also here systematic actions on the thyroid hormone are detected. These are influences in characteristic and predictable ways.

The optimal conditions for therapy with carnitine are still unknown. One does not know yet whether or not a permanant cure using carnitine is possible and if so, in order to achieve lasting results, if it would be necessary to continue administration of carnitine. The suitable doses are still unknown and it is still unclear as to which types of hyperthyreoses will respond to carnitine treatment. In this case, the physician will be the final authority.

The interesting question concerning combined treatment was only recently raised. In the case of severe hyperthyreoses, the corrective operation can often present even a greater danger to the patient (Markkleeberg Hospital, Director: Dr. R. Dreehsler). Often after a few weeks of treatment with carnitine, the symptoms of the disease have been reduced enough so that the operation can be carried out without complications. Earlier, we had already demonstrated that pregnant study animals and their offspring are not damaged by carnitine treatment (11). An hyperthyreotic patient, who was experiencing increasing pain as pregnancy progressed and who was not responsive to other methods of treatment, was again capable of work after carnitine treatment. She gave birth to a healthy child and remained improved in health for a considerable period of time thereafter. Good results have also been achieved with a number of children treated with carnitine. Their state of health remained improved for some time after treatment was stopped.

In several cases, where other forms of therapy had failed, carnitine significantly reduced the symptoms of the disease. We have not yet found a complete failure among the patients that have

been tested and examined. On a number of occasions the results were not as good as desired. This could be the result of a dosage which was not optimal for the conditions. Each case that is encountered appears to be somewhat different. Long-standing cases respond most poorly. The different responses to carnitine can be used to assist in differentiating between the various stages of the disease and for determining the best therapeutic dose. In this way, the patient can be quickly made well again and capable of work. The expense of achieving this goal is unimportant.

SUMMARY

The author furnishes a survey for the bases for the therapeutic effects of L-carnitine in cases of hyperthyreoses. 1 to 3 gm daily taken orally improve many of the pathological symptoms, particularly those which are the results of derangements in the metabolic processes.

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